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ART UNIT	PAPER NUMBER
1641	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/582,090	IMAI, KAZUHIRO	
	Examiner	Art Unit	
	Leon Y. Lum	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *24 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *21 and 22* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 April 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/15/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of claims 1-23 in the reply filed on December 18, 2008 is acknowledged. The traversal is on the ground that Groups I and II, as presented by the Examiner, are related and interdependent. *See* page 2, fourth paragraph. Applicants also traverse on the ground that there is no search burden, given the International Search Authority's examination of all claims together. *See* page 3, first and second paragraphs. Applicants' arguments, however, are not persuasive for the following reasons.

37 C.F.R. § 1.475 governs the national stage requirements for unity of invention. Section (a) explicitly states that unity of invention exists "only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features." (emphasis added). A "special technical feature" is a contribution of the invention over the prior art. Accordingly, claims having unity of invention share two requirements: (1) they have at least one common technical feature and (2) the common technical feature(s) must be free of the prior art. Here, Groups I and II share the following technical features: HPLC, fluorescence detection and fraction collection. Indeed, Group I does not recite the "microcolumn HPLC" or "microfluorescence detector" claimed in Group II. However, these features are not free of the prior art, as evidenced by Schrattenholz. *See* Restriction Requirement, filed November 18, 2008. Applicant has not traversed the Schrattenholz reference.

Accordingly, because Groups I and II do not satisfy the requirements of 37 C.F.R. § 1.475(a), the claims therein lack unity of invention and are properly restricted.

Regarding Applicant's second argument, a showing of a search burden is an element of restriction for a regular U.S. application, not a national stage application. Moreover, Applicant's reliance on 37 C.F.R. § 1.475(c)(3) does not remedy the fact that Groups I and II lack unity of invention under Section (a).

For the foregoing reasons, Applicant's arguments traversing the restriction requirement is not persuasive. Accordingly, the requirement is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

2. The information disclosure statement filed August 15, 2006 is proper and has been considered.

Specification

3. The disclosure is objected to because it does not include a section listing figures 1-12, e.g. "Brief Description of Drawings." Appropriate correction is required.

Claim Objections

4. Claims 21 and 22 are objected to because of the following informalities: "DAASeBD-X" appears as if it should be "DAABSeD-X" and "DAAThBD-X appears as if it should be "DAABThD-X."

5. Claim 22 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. The claim is directed to the same limitation as recited in base claim 21. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claim 1 is vague and indefinite because it is unclear whether the following phrase is directed only to the steps after the term "or" or to the steps before and after the term "or": *collated with a database and provided for structural analysis to identify "he expressed protein and/or peptide*.

Claims 2-14 are vague and indefinite for the same reasons above because the claims are dependent on claim 1.

9. Claim 1 recites the limitation "the fractions" in line 6. There is insufficient antecedent basis for this limitation in the claim. The limitation appears to correspond to the separated peptide fragments, but since it uses a different term, it is unclear whether they are one and the same.

Claims 2-14 are vague and indefinite for the same reasons above because the claims are dependent on claim 1.

10. Claims 2 and 8 are vague and indefinite because they recite the step "collated with a protein and/or peptide fragment database." Base claim 1, however, already recites a database, although this database is not limited to information on protein and/or peptide fragments. Since the step in claims 2 and 8 do not clarify whether the database is the same as the database in claim 1, it is unclear whether one or two steps involving databases are being claimed.

11. Claims 2, 6 and 8 are vague and indefinite because they recite "mass spectrometry or MS/MS analysis." MS/MS analysis – i.e., tandem mass spectrometry, is a form of mass spectrometry. However, as claimed, it appears that mass spectrometry and MS/MS analysis are two separate techniques. Moreover, base claim 1 only recites mass spectrometry. Accordingly, it is unclear whether MS/MS is intended to encompass something other than mass spectrometry. If MS/MS is being claimed as a separate technique, then claims 2, 6 and 8 improperly broaden claim 1.

12. Claim 3 is vague and indefinite for reciting "HPLC/fluorescence detection." It is unclear whether this term is directed to a combination HPLC and fluorescence detection step or to HPLC detection and fluorescence detection in the alternative.

13. Claim 3 is vague and indefinite for reciting the step "collated with a database for structural analysis." Base claim 1 already recites a database, although this database is not limited for structural analysis. Since the step in claim 2 does not clarify whether the database is the same as the database in claim 1, it is unclear whether one or two steps involving databases are being claimed.

14. Claim 5 recites the limitation "the fluorescence-labeled protein and/or peptide" in line 2. There is insufficient antecedent basis for this limitation in the claim. Indeed, base claim 1 does not recite a step in which the protein and/or peptide is labeled, much less with a fluorescent label.

15. Claim 23 is vague and indefinite. The claim recites numerous steps, but it is unclear what the steps are directed towards. For example, take "the protein and/or peptide is identified on the basis thereof." Preceding this phrase is at least three different steps with no clear indication on how they are related to each other. Accordingly, it is unclear what "the basis" is – i.e., the mass spectrometry, the skeleton and electric charge, the fragments, or a combination of them? Moreover, there are two

mass spectrometry steps and it is unclear how they are related to each other – i.e., are they the same step or different steps?

In order to compare the claim with the prior art, the claim is interpreted to mean simply that the protein and/or peptide is identified based on mass spectrometry.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

17. Claims 1-9 and 15 are rejected under 35 U.S.C. 102(e) as being anticipated by Patricelli (US 7,179,655).

i. Independent claims 1 and 15 are anticipated

Patricelli describes a screening and identifying method that comprises, as the screening step, labeling target proteins with a fluorescently labeled activity based probe (ABP), digesting the ABP-labeled proteins and separating the resulting fragments. *See* column 2, lines 35-46 and column 15, lines 53-67. Accordingly, Patricelli teaches "a protein and/or peptide in a test sample is converted to a fluorescent derivative," as claimed. The screening step can include fluorescence detection. *See* column 19, lines

44-56 and column 20, lines 35-43. Patricelli, therefore, teaches "said fluorescent derivative is separated by fluorescence detection."

Regarding the phrase "the fluorescent fraction is applied to mass spectrometry," Patricelli teaches this phrase for the following reason: The identifying step of the method sends separated ABP-labeled proteins for mass spectrometry. *See* column 21,lines 37-50.

Regarding the phrase "the fluorescent fraction is applied to enzymatic hydrolysis, the peptide fragments are separated, and the fractions are applied to mass spectrometry," Patricelli teaches this phrase for the following reasons: Patricelli teaches that "the labeled ABP-active target protein conjugates are most preferably proteolytically digested prior to the next stage of enrichment and/or analysis," (emphasis added) in which the enrichment is the "liquid chromatography and/or electrophoresis" separations. *See* column 5, lines 23-25 and 31-33. The language indicates that proteolytic digestions can be performed after the separation step (i.e., enrichment). The digestion can be performed using trypsin, which, according to the Specification on page 6, section (6), produces enzymatic hydrolysis. *See* column 20, lines 57-59. Accordingly, Patricelli implicitly describes a separation step prior to the enzymatic hydrolysis step.

Patricelli also describes that MS-quantified peptides can be correlated with a sequence database, thereby teaching that the sample is "collated with a database and provided for structural analysis to identify the expressed protein and/or peptide." *See* column 22, lines 31-33.

ii. Claims 2-9 are anticipated

Claims 2-9 are dependent on claim 1 and are taught by Patricelli, as described below. Accordingly, these claims are anticipated by Patricelli.

Regarding claim 2, Patricelli describes that the liquid chromatography can be HPLC. *See* column 20,lines 57-59. Patricelli thereby teaches "the fluorescent derivative is applied to HPLC to capture the fluorescent fraction, the fluorescent fraction is applied to enzymatic hydrolysis." Moreover, as described above, Patricelli describes that MS-quantified peptides can be correlated with a sequence database, thereby teaching "the ion molecular weight data of each of the fragments thus obtained is collated with a protein and/or peptide fragment database for structural analysis."

Patricelli describes HPLC separation combined with fluorescence detection. See rejection *supra*. Patricelli also describes that each of the identification and separation steps can include a chromatography step. *See* column 15, line 60 to column 16, line 2 and column 21, lines 51-60.

Regarding claim 4, Patricelli describes a fluorescent ABP label with an affinity for an active site on a protein. *See* column 9, lines 27-29. Accordingly, Patricelli teaches a "functional group-specific fluorescent reagent."

Regarding claims 5, Patricelli describes electrophoresis separation. *See* column 19, line 50.

Regarding claim 6, Patricelli teaches trypsin, as described above.

Regarding claim 7, Patricelli describes a RP-HPLC. *See* column 20, lines 57-59. Moreover, Patricelli states that a separation technique during the identification step is something that "may be used," thereby indicating that all of the hydrolysis products,

including those not labeled with the fluorescent ABP label, can be applied to mass spectrometry. *See* column 21, lines 51-54.

Regarding claim 8, Patricelli teaches the correlating step described above.

Regarding claim 9, Patricelli describes a biological sample. *See* column 5, lines 38-51.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

19. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Patricelli, cited above, in view of Goodlett *et al.* (US 6,629,040) ("Goodlett").

Patricelli does not explicitly recite a database containing fluorescent reagent-labeled amino acid data. However, Patricelli does disclose a database containing

protein fragment data for comparison purposes. Moreover, Patricelli specifically describes performing an analysis on "labeled peptide samples." *See* column 22, lines 33-38.

Goodlett describes comparing the mass of digested and labeled peptides to those in a database. *See*, for example, claim 7.

It would have been obvious to one of ordinary skill in the art to modify Patricelli's method by including fluorescent-labeled amino acid data in the database, as taught by Goodlett. The skilled artisan would have performed the modification because doing so would provide a database with a more accurate comparison between peptides since the sample peptides are labeled. Moreover, since Patricelli teaches a database, the skilled artisan would have had a reasonable expectation of success in updating the database.

20. Claims 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Patricelli, cited above, in view of Andersson *et al.* (US 6,653,625) ("Andersson").

i. Claim 11 is obvious

Patricelli, described above, teaches a labeling step, a separating step comprising an HPLC separation step prior to protease digestion by trypsin and an identification step comprising a separating procedure prior to mass spectrometry analysis. The separating steps can be performed using HPLC combined with fluorescent detection. Together, these steps comprise a series of four steps that, in sequence, fluorescently label a protein sample, separate the sample using HPLC chromatography with fluorescent detection, digest the sample using trypsin and separate the sample again using HPLC

chromatography with fluorescent detection. Moreover, Patricelli describes a database for comparing experimental results with known peptide structures. A computer is necessary to store the database; hence, Patricelli teaches "one...type of structural analysis device equipped with a database containing data on amino acids labeled with the fluorescent reagent.

Patricelli, however, does not teach a separate physical embodiment to perform each of the four steps above.

Andersson describes a microfluidic system comprising multiple channel parts including a reaction zone for digestion and a separating zone using chromatography. *See* column 7, lines 10-30. However, Andersson does not limit the system to just one reaction zone and separation zone. Indeed, each channel can comprise "one or more channel parts" that function as a reaction zone and separation zone. *Id.* Moreover, the microfluidic system can efficiently transform a sample for mass spectrometry analysis while maintaining a reproducible yield and minimal loss of material. *See* column 3, lines 3-8. The microfluidic system also includes an outlet connected to a mass spectrometry device. *See* column 6, lines 9-22.

Given the foregoing description, it would have been obvious to one of ordinary skill in the art to modify Andersson's device by incorporating a separate chamber for each of Patricelli's steps. The combination, therefore, will produce a distinct labeling chamber, first HPLC separation channel with a fluorescent detector, a digestion chamber and a second HPLC separation channel with a fluorescent detector. The skilled artisan would have been motivated to perform the modification because a

microfluidic device can efficiently transform a sample for mass spectrometry analysis while maintaining a reproducible yield and minimal loss of material. Moreover, Andersson indicates that the microfluidic device can comprise more than one reaction chamber and more than one separation channel. Accordingly, one of ordinary skill in the art would have been guided by Andersson to incorporate a separate chamber or channel for each step described by Patricelli. Moreover, Andersson's device is specifically conditioned to prepare a sample for mass spectrometry analysis. Accordingly, the skilled artisan would have had a reasonable expectation of success.

ii. Claim 12 is obvious

Claim 12 is dependent on claim 11 and recites limitations taught by Patricelli, as described below. Accordingly, claim 12 is obvious over Patricelli in view of Andersson.

Regarding claim 12, since Patricelli teaches that the steps are performed in sequence, it would have been obvious to one of ordinary skill in the art to configure the reaction chambers and channels in Andersson's device to be in series, thereby accommodating Patricelli's sequential steps.

21. Claims 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Patricelli, cited above, in view of Toyo'oka *et al.* (Anal. Chem., vol. 56, pp. 2461-2464 (1984)) ("Toyo'oka").

Patricelli does not describe 4-(aminosulfonyl)-7-fluoro-2,1,3-benzoxadiazole (ABD-F).

Toyo'oka describes ABD-F as an appropriate fluorogenic reagent that can specifically bind to thiol groups, is highly reactive and has good stability. *See* page 2461, abstract and page 2464, left column, second to last paragraph.

Given the foregoing description, it would have been obvious to one of ordinary skill in the art to modify Patricelli's method to include Toyo'oka's ABD-F as the fluorescent label. The skilled artisan would have been motivated to perform the modification based on Toyo'oka's description that ABD-F can specifically bind to thiols and is highly reactive and has good stability. Moreover, since Patricelli indicates that any fluorescent moiety can be used, the skilled artisan would have had a reasonable expectation of success in combining Toyo'oka's ABD-F with Patricelli's method.

22. Claims 16-18, 20 and 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Patricelli, cited above.

i. Claim 16 is obvious

Patricelli, in addition to the subject matter described above, discloses performing the labeling, separation, digestion and MS identification steps on two or more distinct samples. *See* column 3, lines 30-47.

Patricelli, however, does not explicitly teach an HPLC equipped with a fluorescence detector.

Given the foregoing description, it would have been obvious to one of ordinary skill in the art to combine Patricelli's fluorescence detector and HPLC. Patricelli indicates that both devices are used during the separation step, as described above.

Moreover, "equipped" as claimed can simply include attaching the HPCL and fluorescent detector together such that the detector detects eluted fractions from the HPLC – a task that would involve mere routine skill in the art. Indeed, the specification does not limit "equipped" in any manner. Accordingly, the skilled artisan would have been guided by Patricelli to place the HPLC and fluorescent detector together. For the same reasons, the skilled artisan would have had a reasonable expectation of success.

ii. Claims 17-18, 20 and 23 are obvious

Claims 17-18, 20 and 23 are dependent on claim 16 and taught by Patricelli, as described below. Accordingly, the claims are obvious over Patricelli.

Regarding claims 17 and 18, since Patricelli teaches that two quantitative values can be compared, it would involve only routine skill in the art to take a ratio of the two values. Accordingly, the claimed "ratio" step is obvious.

Regarding claim 20, Patricelli teaches biological samples, including cells and tissues. *See* column 5, lines 38-51.

Regarding claim 23, Patricelli teaches mass spectrometry, as described above. Please also refer to the rejection under 112, second paragraph *supra*.

23. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Patricelli, cited above, in view of Srinivasan (US 2007/0065343) ("Srinivasan").

Patricelli teaches employing internal standards comprising fluorescent moieties that are different from those used to label the sample. *See* column 18, lines 30-34. Since the standards are internal, they are considered to be mixed with the sample,

thereby teaching "sample A and sample B are combined." Patricelli also describes mass spectrometry, as described above.

Patricelli, however, does not teach that the combined sample is "applied to two HPLC," as claimed.

Srinivasan describes a method of performing multiple chromographic elutions of a sample, in order to increase sensitivity for a particular analyte of interest. *See* page 2, paragraphs 0013 and 0014.

Given the foregoing description, it would have been obvious to one of ordinary skill in the art to modify Particelli's method with Srinivasan's sequential chromatographic elutions. The skilled artisan would have been motivated to perform the modification since Srinivasan teaches that performing multiple chromatographic elutions will increase the sensitivity of the assay. Moreover, since Patricelli teaches chromatographic elutions, the skilled artisan would have had a reasonable expectation of success in adding an extra chromatographic elution.

Allowable Subject Matter

24. Claims 21 and 22 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

25. Claims 1-20 and 23 are rejected. Claims 21 and 22 are objected to.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leon Y. Lum whose telephone number is (571) 272-2872. The examiner can normally be reached on Monday to Friday (8:30 am to 5:00 pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark L. Shibuya can be reached on (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leon Y. Lum/
Examiner, Art Unit 1641

/Nelson Yang/
Primary Examiner, Art Unit 1641